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| EXAMINER | |
|---|---|
| WEBB, WALTER E | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/580,098 | MCCLUSKEY ET AL. | |
| | Examiner | Art Unit | |
| | WALTER E. WEBB | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,26,56,57,60,62,63,65,66,69,70,72,73,75-79,81 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,26,56,57,60,62,63,65,66,69,70,72,73,75-79,81 and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/27/2009, 9/3/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/3/2009 has been entered.

Applicants' arguments, filed 9/3/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

### *Claim Objections*

Claim 86 is objected to because of the following informalities: “prophalaxis” is misspelled. It should be “prophylaxis”. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112—previous*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 26, 56, 57, 60, 62, 63, 65, 66, 69, 70, 72, 73, 75-79, 81 and 86 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

**Written Description Rejection**

Claim 86, continues to recite the term "prodrug."

The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See, e.g., In re Wilder, 22 USPQ 369, 372-3 (Fed. Cir. 1984). (Holding that a claim was not adequately described because the specification did 'little more than outline goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.')

Mere indistinct terms (such as "prodrug" used herein), however, may not suffice to meet the written description requirement. This is particularly true when a compound is claimed in purely functional terms. See Univ. of Rochester v. G.D. Searle, 69 USPQ2d 1886 (CAFC 2004) at 1892, stating:

> The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its functioning of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is,

> usually does not suffice…. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. (Emphasis added).

Conversely, a description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. See Univ. of Calf. V. Eli Lilly, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under Section 112, ¶ 1, by showing the enablement of a representative number of species within the genus.

A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. *If the genus has substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus*. See MPEP 2163. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any *combination of such identifying characteristics that distinguish the claimed invention from other materials* and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. MPEP 2163.

Here, the specification does not provide a reasonably representative disclosure of useful prodrugs generally, a potentially huge genus inclusive of many different compounds having widely divergent structures and functions. Specifically, the specification discloses only a limited number of species at pages 44-45, Table 2 and

Table 3, and these are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

**Enablement Rejection**

Claims 1, 26, 56, 57, 60, 62, 63, 65, 66, 69, 70, 72, 73, 75-79, 81 and 86 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for **prophylaxis** or treatment of disease mediated by dynamin-dependent endocytosis.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method for prophylaxis or treatment of epilepsy in a mammal by administering a compound of formula I. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable

nature of the art. As illustrative of the state of the art, the examiner cites Duncan et al., (The Lancet 2006).

Duncan et al. discloses that drug treatment of epilepsy is effective in only 60-70% of individuals and that the aim of the treatment is to control the size of the seizures as quickly as possible. (See Drug Treatment at pg. 1092.) They also teach that for some a cure is possible through a neurosurgical procedure. (See abstract.) Since drug treatment of epilepsy is generally effective in 60-70% of patients, the artisan would not accept that epilepsy can be prevented with applicant's claimed compound, especially since there is no known drug that is effective for preventing or prophylaxis of epilepsy.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention" or "prophylaxis", the terms will be interpreted expansively. The terms, generally, may vary widely in meaning, from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the disease, it will not worsen; or that following its treatment, it will not recur. While such "prevention" or "prophylaxis" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for prophylaxis of epilepsy, other than *in vitro* data showing GTPase binding assays, and endocytosis. The latter is corroborated by the working examples. (See pp. 22-30).

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for prophylaxis of epilepsy as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

**3)Scope of the diseases being treated**

Given the unpredictable nature of treating epilepsy cited in the art above, one of ordinary skill in the art would not accept on its face that applicant's claimed active agent

could treat diseases or conditions in a mammal mediated by dynamin-dependent endocytosis in general. Dynamin is part of a family of GTP-binding proteins with multiple functions affecting many processes throughout the body. There is no support in applicants disclosure for the breadth of diseases related in any way to dynamin-dependent endycytosis. There is also no guidance for specifically treating epilepsy. Epilepsy is merely cited among a laundry list of diseases of which the instant compunds "may be useful" (see pg. 18, line 15 and 25-30). The artisan would be subject to undue experimentation in determining which diseases are related to dynamin-dependent endocytosis as well as determining which of the diseases found showed some sensitivity to a compound of formula I. Applicant's claims are not commensurate in scope with applicant's disclosure.

**4)Scope of active agents**

The specification does not adequately enable a person having ordinary skill in the art to use the claimed invention in light of the scope of compounds formula I, which, as claimed, have a plethora of functional groups including a vast range of heteros. There is no reasonable basis for assuming that myriads of compounds not made and thus not tested will share the requisite minimum activity needed to practice the invention, especially when receptor binding is generally known to be structure sensitive. See In re Fisher, 166 USPQ 18, and In re Surrey, 151 USPQ 724 in regards to sufficiency of disclosure in cases directed to structure sensitive arts. The Examiner acknowledges that the applicant is not required to test every compound, but further guidance is need in order for the artisan to practice the invention without undue

experimentation. Applicant's disclosure is inadequate as to directing or guiding how dimeric tyrophostin can be employed to predictably inhibit dynamin activities other than GTPase activity or how other compounds represented by formula I can predictably inhibit the GTPase activity and other activities of dynamin. For example, it is known in the art that dynamins play a role in cell growth, cell spreading, and neurite outgrowth. (See Urrutia et al., Proc. Natl. Acad. Sci. 1997, at abstract and Multiple Functions for the Dynamin Family at pp. 382-383.)

***Claim Rejections - 35 USC § 102--New***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 26, 56, 57, 60, 62, 63, 65, 66, 69, 70, 72, 73, 75-79, 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Gazit et al., (Journal of Medicinal Chemistry 1996) as evidenced by De Witt et al., (Free Radical Biology & Medicine 2000) and Sahni et al, (The Journal of Biological Chemistry 1996).

Gazit et al. teach the elected species of formula I, Bis-T23 (see Table 1 structure number 5 at page 4907). The reference teaches that this compound and compounds like it, known as tyrphostins, are potent inhibitor of EGF receptor tyrosine kinase. (See abstract.) To demonstrate the biological effect of Bis-T23 on EGF receptor tyrosine kinase, HER-14 cells were contacted with Bis-T23 (see Table 1 at pg. 4907). The

reference also teaches that these compounds can selectively inhibit different PTK's, such as Src family kinases.[2] They teach that their dimeric inhibitors are expected to have enhanced efficacy as compared to the monomeric inhibitors. (See Introduction, 4th paragraph.)

De Witt et al. and Sahni et al. are cited to show that HER-14 cells contain dynamin and that dynamin is instrumental to a particular function of these cells. De Witt et al. teaches methods of inhibiting EGF receptor endocytosis performed by HER-14 cells (see Abstract). Sahni et al. teaches that dynamin is involved in clathrin-mediated endycytosis in non-neuronal cells (see pg. 33146, right paragraph, lines 14-15). It is gleaned from these references that HER-14 cells comprise dynamin which functions to mediate its receptor endocytosis. This is also supported in applicant's specification at pg 29, section 1.2.5, where an experiment was discussed showing bis-tyrphostin blocks the dynamin II-mediated receptor mediated endycytosis of transferrin into HER-14 cells.

The Gazit et al. reference is anticipatory insofar as it meets the method step of claim 1, i.e. contacting a cell with a compound of formula I.

### *Claim Rejections - 35 USC § 103--New*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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[2] Here the reference directs the reader's attention to references 4-6. Reference 4 has been provided for support.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 26, 56, 57, 60, 62, 63, 65, 66, 69, 70, 72, 73, 75-79, 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gazit et al., (supra) as evidenced by De Witt et al., (supra) and Sahni et al, (supra). in view of Ahn et al., (Journal of Biological Chemistry 1999.)

This presumption is made here purely *arguendo*, in the interest of completeness of prosecution, since as stated above the examiner believes the reference to be anticipatory.

Gazit et al. differs from the instant claims insofar as it does not teach inhibiting dynamin GTPase activity.

Ahn et al. teach that Src-mediated tyrosine phosphorylation of dynamin is essential for its function in clathrin mediated G protein-coupled receptor endocytosis. (See abstract.)

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to inhibit dynamin activity with the compound of Gazit, since the compound inhibits Src tyrosine kinase and Src tyrosine kinase phosphorylates dynamin, the function of which is essential for dynamin endocytosis activity. Ahn shows in figure 1 at page 1186 that inhibition of the Src tyrosine kinase inhibits the activity of dynamin. Because the compounds of Gazit also inhibit Src tyrosine kinase, they would also inhibit the activity of dynamin.

***Response to Arguments***

In regard to the written description rejection, applicant argues that based on the disclosure provided at page 16, lines 13-27, and Examples 3 and 4 of the specification, applicant is in possession of "prodrug". However, the disclosure makes no correlation between structure and function. Nor does it describe how the groups, i.e. carbonates, carbamates, etc., are attached to the core structure. The limited number of species are not viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

It should be noted here that applicant mentions a declaration submitted under Rule 1.32 by Prof. Robinson, however no such declaration has been submitted.

In regard to the scope of enablement rejection, applicant argues that the *in vitro* utility reasonably correlates with an *in vivo* activity. However, given the unpredictability in treating epilepsy and applicants lack of evidence demonstrating prophylaxis or prevention thereof, a clear burden of undue experimentation would be placed upon the

skilled artisan in order to practice the full scope of the presently claimed invention. Applicant is also reminded that the arguments of counsel cannot take the place of evidence in the record (see MPEP 2145 relying on *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965)). Applicant also relies in the alleged declaration by Professor Robinson in support of these arguments. These arguments are not considered here since no such declaration has been submitted.

## ***Conclusion***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612